PhRMA Scientific Comments for Docket # 2004N-0355

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA members invested an estimated $33.2 billion in 2003 in discovering and developing new medicines. PhRMA companies are leading the way in the search for new cures.

PhRMA welcomes the opportunity to be a constructive participant in the discussion of scientific issues for follow-on biologics and commends the Food and Drug Administration (FDA) for holding this public stakeholder workshop on scientific issues. PhRMA believes that the paramount goal of discussions must be to preserve the health and safety of patients and patient confidence in their medicines. PhRMA thus continues to support sound, science-based regulatory decisions for all drugs and biologics. All pharmaceutical products, whether small molecule or biologic, innovative or follow-on, must be subject to the same high standards of safety and efficacy.

Unlike typical small-molecule drugs, biologics raise special concerns due to their complexity and the close relationship between a biologic's manufacturing process and its clinical attributes. Any regulatory approach to follow-on biologics must address these concerns from a sound scientific perspective to ensure that the high standards of safety and efficacy now applied are not compromised. Based on the current state of scientific knowledge, all follow-on biologic applications should be supported by appropriate studies using the investigational follow-on product. The study requirements applicable to

different products can be expected to vary based on relevant therapeutic, manufacturing and other concerns as evaluated based on evolving science. While these considerations may permit the approval of follow-on biologics based on scientifically-justified different data sets from original innovative approvals, each follow-on product should be supported by a full chemistry, manufacturing, and controls section, and by data generated from appropriate preclinical work, and clinical safety and effectiveness trials, and be followed up by robust post-market surveillance.

In addition to the scientific issues that we address here, there are substantial legal and policy concerns that need to be considered, particularly with respect to the protection of trade secrets and other intellectual property rights that support innovation. These are addressed in the comments that PhRMA is submitting to Docket No. 2004P-0171 and found here as Attachment B.

In the meeting announcement, FDA used the term "follow-on protein pharmaceutical products." Throughout these comments we will use the term "Follow-on Biologics" to mean follow-on versions of "biologics, including therapeutic proteins, developed and manufactured by a company unrelated to the innovator, produced either through recombinant technologies or from natural sources." Our comments will address the following three issues: (1) Analytical Characterization and Manufacturing; (2) Safety, especially Immunogenicity; and (3) Therapeutic Equivalence. Throughout, we will emphasize the special considerations for biologics, contrasting these with small molecule drugs, to highlight the unique challenges associated with producing safe and effective follow-on biologics.

Analytical Characterization and Manufacturing Quality, Process and Standards

The term "follow-on biologic" implies abbreviated approval requirements for the follow-on product predicated on the sameness of the product. However, there are significant analytical challenges to achieving adequate characterization of biologic products to establish the identity of the manufactured products. These challenges reflect to a large extent the significant physico-chemical differences between biological drug products and small molecule drug products.

There are a number of differences between a biological drug product and a typical small molecule drug product that are reflected in the analytical testing methodologies employed to assure quality. Biologics differ substantially in physical characteristics from small molecules. The size and complexity of a biological molecule is typically 1000 times that of a small molecule drug. While a single chemical formula can usually adequately describe the molecular structure and composition of a small molecule made up of tens to hundreds of atoms, this is not possible with a protein product, made up of tens of thousands to millions of atoms.

The analytical capability to demonstrate true identity, or pharmaceutical equivalence, between innovator and follow-on biologics is currently limited, at best. The chemical composition and structure of a small molecule drug active ingredient can be determined precisely by widely accepted physical and chemical assays. On the other hand, characterization of a biologic with the same degree of precision is typically impossible because of its structural complexity and because the final product usually is a heterogeneous mixture of molecular species. Many analytical tools for characterizing biologics currently have a low resolving power to detect subtle, but potentially important,

changes. When changes occur, it is often difficult to assess how they may impact clinical performance or immunogenicity. Even when the analytical resolving power improves, the new information may make the existing heterogeneity of the biologic more apparent.

To achieve identical composition between biologics produced by unrelated manufacturers is virtually impossible because of the nature of biological manufacturing where the manufacturing process determines the product characteristics. While the manufacturing process for a chemical drug product would typically involve up to several dozen discrete, linear steps progressing in a predictable way when the environmental conditions (time, temperature, mixing) are well-controlled, the manufacturing processes for biologics are based on the synthetic capabilities of living cells that have inherent metabolic and synthetic variability. Using a living organism to produce a biological product involves hundreds to thousands of interconnected steps in complex metabolic pathways which are very sensitive to environmental perturbations; one need only envision the pathway for synthesis of one kind of amino acid to see this complexity. To handle the complexity of the biological manufacturing process, extensive analytical testing is done at key process steps using validated assays that are often proprietary, with appropriate sample qualification to ensure that the process intermediates are suitable for progressing to the next step. Each biologic manufacturing process will result in a unique product, including the mixture of active and inactive molecules and the levels of process- and product-related impurities. Small differences between manufacturing processes may cause significant differences in the clinical properties of the products. Chemically and pharmaceutically identical biologics will not result from unrelated manufacturers.

Throughout the development of both innovator and follow-on biologics, a complete and thorough body of knowledge is generated on the process and product, beginning with the genetic constructs, expression systems, and cell banks, and continuing through fermentation or cell culture, and purification. The process knowledge of the manufacturer is important to ensure that product quality is not compromised. Similarly, detailed knowledge of the raw materials, reagents, and components used during the manufacture are critical to controlling the ultimate quality of the drug substance. Each cell line/vector combination together with its manufacturing process will result in a unique drug substance. Environmental conditions during the manufacture of the drug substance are critical in determining the degree of heterogeneity of active and inactive molecules. Each manufacturing process will affect the ultimate potency of the drug, including the levels of process- and product-related impurities.

Process validation for biologics is more complex than for chemical drug products due to the number of process steps and the sensitivity of the biological process to external variations, e.g., batches of raw materials, working cell banks, harvest times. The quality of each component of the process including the raw materials, reagents, and excipients, must be controlled. Samples taken throughout the various stages of the manufacturing scheme need to be tested by validated analytical methods. Validation of an adequate control strategy, including in-process controls, can only be determined once a manufacturer has gained thorough knowledge of the product and understands how the manufacturing process impacts the resulting product. Therefore, while thorough characterization of the physical, chemical, and bioanalytical properties of the drug substance and product are essential, these tests alone can never assure a quality product.

The commercial biologic product must be tested to meet predefined criteria to demonstrate that the product batch is representative of the material tested in the clinic and demonstrated to be generally safe and effective. These specifications are realized through knowledge of the clinical performance, the process development experience, analytical methods design and validation, and in-process testing to define the product. Biologics are approved by the regulatory authorities in the context of this entire body of knowledge. One cannot standardize the analytical testing and specification ranges of the biologic through monographs because each manufacturer has a different proprietary process and different reference standards linked to their clinical experience.

The manufacturing and analytical challenges in dealing with the complexity and heterogeneity of biologics are the same for a follow-on as for an innovator manufacturer. Innovator pre-clinical safety, clinical trial, process validation and development data support only the degree and forms of product heterogeneity of the innovator product. The question is how to determine the significance of this heterogeneity for product quality for the follow-on biologic.

There is no way to know what is needed to establish a set of specifications for any product without clinical studies to demonstrate that given levels of impurities are safe, and that doses selected are safe and effective. From these clinical data, specifications are tailored to each product and process. There is abundant evidence that products from different processes often have different impurity profiles, and hence the analytical methods and specifications for purity and impurity levels will need to be different and appropriate to each product and process.

FDA has faced the question of controlling changes in manufacturing process by

innovators ("FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products," April, 1996). In response to questions from the Senate Judiciary Committee, FDA has recently discussed that this guidance was intended to address changes in which a single manufacturer makes changes to its own manufacturing process and must demonstrate comparability between the "old" and "new" products. When considering a process change for an innovator biologic, the manufacturer reviews an extensive body of knowledge generated over the life of the product, which allows for an understanding of the significance of differences that may be detected and provides a baseline for comparison of changes. The knowledge gained about the manufacture of the innovator biologic includes an extensive database of every step in the manufacturing process, established in-process controls, and defined reference standards to allow for detailed comparison between product made before and after a manufacturing change. Developers and manufacturers of follow-on biologics do not have access to the same extensive data or proprietary analytical methodologies to allow for the same scientific comparison. Conclusions regarding similarity or differences cannot be drawn across unrelated manufacturers. Therefore, it would not be appropriate to apply comparability principles designed as a means to assess changes made by the innovator of a biologic as the basis to approve a follow-on biologic developed and produced by another, unrelated manufacturer. In response to questions from the Senate Judiciary Committee, FDA has recently confirmed that while the science underlying these principles may have applicability to Follow-on Protein Products, the concept of comparability will only apply under special circumstances.

The example of Raptiva presented by Genentech at the September 14-15 Workshop demonstrates that even under carefully controlled conditions for scale-up, changes made when the product was transferred from Xoma to Genentech resulted in differences in clinical performance. In this case the analytical and animal studies did not show any differences between the products. It was only in human pharmacokinetic (PK) studies that differences were first detected, and it required an additional Phase III clinical study to demonstrate the dosing and effectiveness of the scaled up product.

In a brief summary to this point, biologic drugs are orders of magnitude more complex than small molecule drugs. Identity between two products manufactured by different processes can not be verified for most protein drugs using current analytical methods. Safety and efficacy of the final product are dependent upon the manufacturing process and are exquisitely sensitive to small changes in biological processes It is difficult to impossible to predict the effect of these small changes to biological processes and products — experience counts.

Safety and Immunogenicity

Manufacture and clinical testing of biologic drugs must include additional safety control measures beyond those used for small molecule drugs. For example, adventitious agent control is a critical element to manufacture of biologics and is done both on input raw materials and output fluids from the cell culture. This type of safety assurance is not often required in the manufacture of chemical drug products because the processing environment is inhospitable to the propagation of most adventitious agents, and the characteristics of most chemical drugs facilitate terminal sterilization. By contrast, the

biosynthetic processing environment can directly support the inadvertent growth of adventitious agents, and most biological products cannot be sterilized terminally without loss of bioactivity.

Safety concerns related to a biologic can involve a wide array of effects on multiple target organs, in addition to the more general concerns related to immunogenicity. Product-specific concerns are heightened for molecules with pleiotrophic biological activities and a complicated or unknown mechanism(s) of action. Preclinical safety assessments of biologics are more difficult and complicated than for small molecules because of unique issues. However, based on the current state of scientific knowledge, all follow-on biologic applications should be supported by appropriate preclinical safety studies using the investigational follow-on product, as described in ICH S6. Because fewer pre-clinical studies and animal pharmacology/toxicology models are routinely available to assess safety of biologics than for small molecules, safety assessments for a biologic must depend more heavily on clinical studies.

Assessment of immunogenicity is a key component for determining safety of biologics. It is well established that the immune system is exquisitely sensitive to and capable of responding to subtle characteristics of a biologic that may not be detectable by analytical methods. Such an immune response can stimulate the production of antibodies that can bind to the therapeutic protein and inactivate it or otherwise alter its activity. In these cases, the product no longer provides effective therapy to the patient and the disease progresses. If the therapeutic product is similar to a naturally-occurring protein, the antibody may bind to and inactivate the native protein, making the underlying disease

even worse or causing other serious side effects. In other cases, the induced antibodies may have no observable effect.

There are many examples of biologics that have resulted in problematic immune responses in patients. In some cases, these problems were detected in clinical trials during the development process, leading to the termination of the product's development. In other cases, the problem was recognized only after the product was commercially launched. In yet other cases, problems arose after manufacturing changes were made. Sometimes the potential cause of the immunogenicity was determined; in other cases, it remains unknown.

Few pre-clinical models effectively predict human immunogenicity for human proteins, a concept that is recognized in ICH S6. For example, there are many proteins that are non-immunogenic in humans (e.g., tissue plasminogen activator, most monoclonal antibodies, erythropoeitin), and yet they stimulate major immune responses in animals on repeat administration. On the other hand, while alpha-interferons (like most human proteins) are highly immunogenic in most animals on repeat administration, they produce no immune response in some indicated patient populations, but in other patient populations they produce substantial (30% or more) incidence of neutralizing antibody that results in clinical relapse.

An example of serious side effects from antibodies cross-reacting and interfering with the native protein was presented at the September 14-15 Stakeholder Workshop. Johnson and Johnson described their experience with EPREX (erythropoietin) and Pure Red Cell Aplasia (PRCA). The immune response to this product was unpredictable and took extensive research to understand. For a long while the cause of this immunogenicity

was not understood.

As noted earlier, unlike small molecule drugs, the complex manufacturing process for a biologic is a significant determinant of that product. Even a small change to a well-established manufacturing process for a biologic can result in unpredictable and undetectable changes to the product, which can have marked clinical consequences. Because a follow-on biologic, by definition, will be produced with materials and a manufacturing process that are different from the innovator's, unpredictable and undetectable differences are likely between the innovative and follow-on products.

Unfortunately, assays to detect antibodies are not standardized and remain highly individualized with regard to sensitivity and variability. Only well-established, high quality and sensitive antibody assays can be depended upon to identify differences in products, and these comparisons must be performed with both products compared in the same clinical study using the same antibody assay.

There is broad scientific consensus that problems with immunogenicity cannot be dependably predicted from physiochemical characterization, epitope analysis, or animal studies. While some product characteristics such as aggregation and impurities may play a role in increasing the likelihood of an undesirable immune response, the multitude of factors triggering antibody production remains poorly understood and largely unpredictable. Of particular concern is the potential for contaminants and impurities to act as adjuvants to increase the immunogenicity of a biologic.

The lack of reliable, non-clinical models to predict the immunogenicity of a biologic in patients underscores the absolute necessity for immunogenicity testing in clinical trials for all biologics -- follow-on and innovative. Antibody evaluation must be

conducted over the course of treatment in the intended patient population because it is well-established that the incidence of an immune response and the consequences vary from one population to another. Consequently, immunogenicity testing of a follow-on biologic must be as rigorous as that required by today's standards for an innovative biologic.

The number of patients in clinical studies that should be tested for immune responses, as well as the frequency of testing, must be adequate in order to ensure a low risk to patients taking either an innovator product or a follow-on biologic; there can be no shortcut. It does not follow that if an immunogenic event associated with an innovative product is too rare to be detected in even a full clinical program, then clinical testing for its follow-on should be minimal. A rare or unusual immunogenic event triggered by one factor related to one biologic, does not guarantee that such an event will be just as rare when triggered by another factor related to the follow-on product.

A "risk-analysis assessment" has been proposed by the FDA with regard to immunogenicity testing for follow-on protein products. While such an approach is reasonable in the context of new standards for risk management for all products, there should be no differential application of any of these principles and testing requirements regarding immunogenicity to innovative and follow-on products that might otherwise result in an increased risk being assumed by patients taking a follow-on product. Furthermore, any rationale for minimal or reduced, clinical testing of immunogenicity would leave the true "testing" to after marketing. Post-marketing surveillance cannot replace the scrutiny that is applied to testing done in pre-market clinical trials. Patients taking marketed products rightly assume that the risk associated with their medicine has

been comprehensively evaluated by the testing conducted before approval.

Therapeutic Equivalence

Therapeutic equivalence is the basis for substitution of one product for another by a pharmacist. The underlying assumption is that therapeutically equivalent products are interchangeable. In other words, therapeutically equivalent products are assumed to have the same safety and efficacy profiles.

The starting point for therapeutic equivalence is a showing of pharmaceutical equivalence and bioequivalence. Pharmaceutical equivalence is very difficult (and in many cases, impossible) to demonstrate for biologics, and therefore therapeutic equivalence will not be demonstrable either. Even if pharmaceutical equivalence and bioequivalence could be shown, however, these criteria alone are not adequate to assure true therapeutic equivalence for biologics. Pharmaceutical equivalence, when achievable, plus bioequivalence testing, do not support the assumption of comparable safety (including immunogenic) and efficacy profiles and, hence, do not support an assumption of therapeutic equivalence of biologics. For biologics, in addition to pharmaceutical equivalence and bioequivalence, comparable safety and efficacy must be shown with well-designed, adequately powered clinical studies in order for two products to be deemed therapeutically equivalent (and substitutable, one for the other).

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In summary, PhRMA welcomes the opportunity to be an active participant in the discussion of an approval pathway for follow-on biological products. We have

highlighted some of the many scientific and safety challenges in the manufacture and characterization of all biologics, and how these pose additional challenges in contemplating an abbreviated approval pathway for a follow-on product. The very nature of biologics themselves and the current limitations of science are at the heart of these: the tight dependence of product quality and clinical performance on manufacturing process, the complexity and heterogeneity of biological systems and their products, and the unpredictable response of the immune system. Because of these properties, the safety and efficacy profiles for an innovator product should not be assumed to apply to a follow-on biologic produced by a different manufacturer, and attempts to do so raise important patient safety concerns. Based on the current state of scientific knowledge, all follow-on biologic applications should be supported by appropriate studies using the investigational follow-on product. Each follow-on product should be supported by a full chemistry, manufacturing, and controls section, and by data generated from appropriate preclinical work, and clinical safety and effectiveness trials, and be followed up by robust post-market surveillance.

PhRMA thanks the FDA for holding the public workshop and for giving us the opportunity to address the scientific issues for follow-on biologics. We recognize this that the September 2004 Stakeholder's Workshop and the associated docket are a first step and look forward to more in-depth discussion of the relevant issues, including discussion of the scientific and regulatory challenges in the proposed 2005 workshop. PhRMA believes that the paramount goal of these discussions must be to preserve the health and safety of patients and patient confidence in their medicines.